

REMARKS

Status of the Claims

No Claims have been amended or canceled. Claims 26-31, 33, and 35-39 are in the case.

Rejections Under 35 USC §112, First Paragraph

The Action rejects all of the claims as failing to comply with the enablement requirement of section 112, first paragraph. The Action argues: “the specification does not provide a method of treating prostate cancer or any neoplastic disorder by administering to the subject an anti-caveolin antibody.”

The claims are fully enabled by the Specification.

The Specification includes more than adequate support to teach one of skill in the art how to practice the claimed inventions. The Specification teaches, for example, (i) caveolin is increased in metastatic prostate cancer ([0080] and as reported in Yang et al., 1998) (ii) caveolin is increased in androgen insensitive cancer [0117] and (iii) inhibition of caveolin restores androgen sensitivity *in vivo* when combined with castration therapy *in vivo* (Fig. 1).

Caveolin increases in metastatic human prostate cells.

The Specification states in [0017] that caveolin expression increases in metastatic human prostate cells as compared to primary tumors and agents, and blocking the activity of caveolin in metastatic cells or cells predisposed to metastasis would be useful in treatment of human prostate tumors. The Specification further describes treating prostate cancer and metastatic prostate disorders by administering an anti-caveolin antibody, at least at paragraphs [0019] [0077] [0079] [0080] [0087] [0090] and [0095], all of which teach one of skill in the art that suppression of caveolin activity is useful in the treatment of metastatic prostate cancer and prostate neoplasia with potential to progress to become metastatic. Although the *in vivo* data were obtained by genetic suppression of caveolin, either by antisense or knockout constructs, one of skill in the art

clearly understands that the suppression of caveolin activity can also be achieved by the use of antibody therapy as described. The use of anti-caveolin antibodies in inhibition of metastasis in prostate disease is thus fully enabled.

Inhibition of caveolin restores androgen sensitivity to prostate cancer.

Furthermore, the method of claim 35, inhibiting caveolin activity concurrently with androgen depletion therapy, is also fully enabled by the Specification. It is an important aspect of the disclosure that inhibiting expression or activity of caveolin restores androgen sensitivity to prostate cancer. It is well known that prostate cancer is androgen dependent, or in other words, prostate cancer will not grow in the absence of androgen, and a primary treatment for prostate cancer includes androgen deprivation. Certain tumors, however, become androgen insensitive and no longer require androgen to grow. When this occurs, the tumor no longer responds to one of the most effective available treatment options. Restoring androgen sensitivity by concurrently suppressing caveolin and androgen is an important and novel contribution to the art. This effect and combination therapy are described in the Specification at least at paragraphs [0021] [0079] [0081] [0085] and [0117]. The treatment of prostate cancer by suppressing caveolin with an anti-caveolin antibody in conjunction with reducing androgen levels, therefore, is fully enabled by the Specification.

None of the cited prior art refutes the Specification's teaching that inhibition of caveolin with antibody therapy is an effective treatment for prostate cancer.

The Action argues that treating tumors with antibodies is unpredictable and that there is not "convinced evidence that caveolin is directly related with tumorigenesis and is useful therapeutic target." On the contrary, the current state of the art has greatly reduced the relevancy of the prior art relied upon by the Action. Several antibodies have been approved for cancer treatment, and studies show that caveolin is directly linked to prostate cancer progression.

Monoclonal antibodies are increasingly recognized as important agents for the treatment of cancer.

The Action relies upon previously cited articles suggesting the “unpredictability of treating tumors with antibodies.” Applicant respectfully reasserts and relies upon the specific arguments made with respect to each reference in the previous response. None of the cited art, either alone or in combination refutes the description in the Specification that inhibition of caveolin with antibody therapy would be beneficial in the treatment of neoplastic disease of the prostate, and more particularly that such treatment would inhibit metastasis as in claim 26, or restore androgen dependence as in claim 35. The references relied upon by the Action in no way provide support for a blanket rejection of all treatments of cancer with antibodies. Furthermore, one of skill in the art would not rely upon such references to determine whether the Specification was enabled the use of anti-caveolin antibodies for the treatment of prostate cancer. More recent reviews are more accurate reflections of the state of the art of antibody therapies for cancer. For example, Strome, et al., review six monoclonal antibodies that have been approved by the U.S. Food and Drug Administration for use in cancer therapy. *A Mechanistic Perspective of Monoclonal Antibodies in Cancer Therapy Beyond Target-Related Effects*, The Oncologist, 12:1084-95, (2007) (see Table 1 for list of six antibodies approved by the FDA) (attached as Exhibit 1). Strome conclude: “mAbs [Monoclonal antibodies] represent an important advance in the treatment of certain hematologic malignancies and solid tumors. Unlike many small molecules, mAbs offer unique target specificity. **The field has evolved rapidly in recent years, and now it is much easier to create mAbs against a variety of targets of potential relevance to tumor growth and survival.**” Strome at 1092, emphasis added. Likewise, Sharkey, et al., similarly describe the state of antibody cancer treatments: “Immunotherapy of cancer has been explored for over a century, but it is only in the last decade that various antibody-based products

have been introduced into the management of patients with diverse cancers. **At present, this is one of the most active areas of clinical research, with eight therapeutic products already approved in oncology. Antibodies against tumor-associated markers have been a part of medical practice in immunohistology and *in vitro* immunoassays for several decades, have even been used as radioconjugates in diagnostic imaging, and are now becoming increasingly recognized as important biological agents for the detection and treatment of cancer.**” *Targeted Therapy of Cancer: New Prospects for Antibodies and Immunoconjugates*, CA: A Cancer Journal for Clinicians, 56:226-43, abstract (2006) (attached as Exhibit 2). These articles are but two examples of many publications describing the development and use of antibodies in cancer treatment. Notably, at least six antibodies have endured and survived the rigorous and thorough testing process required for Food and Drug Administration approval. Thus, in light of these reports on the state of the art, one of skill in the art would immediately recognize that monoclonal antibodies are useful in the treatment of cancer and would recognize the Specification as enabling for such treatment.

The fact that the FDA has approved at least six antibodies for the treatment of various cancers refutes the Action’s general argument that treating cancer with antibodies is unduly “unpredictable.” There is always an element of unpredictability in the development of biological therapies because biological systems are complex and interrelated, but such unpredictability does not present a rational basis for rejecting an otherwise enabled claim. To the contrary, as evidenced by the FDA’s approval, antibodies have been shown to be predictably therapeutic in treating cancer.

Studies confirm that caveolin is directly related to tumorigenesis.

The Action also argues: “the prior art does not provide convinced evidence that caveolin is directly related with tumorigenesis and is useful therapeutic target . . . the prior art has not settled the question of the biological function of caveolin in neoplastic disorder comprising prostate or breast cancer.” In response, Applicant submits a peer-reviewed, published article co-authored by the inventor Timothy C. Thompson which confirms the Specification’s disclosure with respect to the role of caveolin in prostate cancer. Tahir, et al., *Tumor Cell-Secreted Caveolin-1 Has Proangiogenic Activities in Prostate Cancer*, Cancer Research, 68:731-39 (February 1, 2008) (attached as Exhibit 3). In this article, the authors “examined the association between cav-1 expression and prostate tumor-associated angiogenesis” by generating an LNCaP (human prostate adenocarcinoma) tet-on cav-1 cell line (referred to as LNTB25cav) in which cav-1 was regulated by doxycycline. Tahir at 6. In one assay, LNTB25cav tumors were established as subcutaneous xenografts in nude mice. *Id.* at 7. Tumor-bearing mice were treated with either doxycycline or a control solution. *Id.* The doxycycline induced cav-1 expression in the tumors and resulted in significantly greater tumor volumes. *Id.* at 7 and Fig. 6. These data confirm that caveolin expression contributes to tumor growth. In a second assay, the LNTB25cav cells were injected into the tail veins of nude mice to study lung metastases. The test group was treated with cav-1 inducing doxycycline for 42 days. When compared to the control group, “the number and frequency of lung metastases in doxycycline-treated [cav-1 induced] animals significantly exceeded results in the control group . . . and their average size was clearly larger in doxycycline-treated mice.” *Id.* at 7 and Fig. 6. These data confirm that caveolin expression contributes to tumorigenesis. Thus, taken together, these data confirm the Specification’s disclosure that caveolin is directly related to tumor growth and size.

The Action also argues that the specification is not enabled for inhibiting caveolin concurrently with androgen depletion therapy. The argument, though, is based on the Action's previously-addressed assertion that "applicant has not provided the enablement disclosure for the claimed method of treating prostate disorder using anti-caveolin antibody." Applicant respectfully submits that the information provided above to overcome the enablement rejection for treating prostate cancer with anti-caveolin antibodies also overcomes this rejection. Furthermore, Applicant reasserts arguments made in previous responses that treatment of prostate cancer with androgen depletion therapy is well-known in the art. Thus, Applicant respectfully requests withdrawal of the rejection.

The references cited in the Action do not reflect the state of the art with respect to treating prostate cancer with caveolin.

Further, the Action reasserts previous arguments that cited references—Weiner, Dillman, Jain, and Nelson—support the Examiner's position that treatment of prostate cancer with caveolin is not enabled because of the "unpredictability" involved. In light of the submitted articles that more accurately reflect the current state of the art with respect to treating cancer with antibodies, and in light of the submitted assays showing that abnormal caveolin expression contributes to tumor growth and size, Applicant respectfully submits that any undue unpredictability suggested by the references is outdated and not relevant. In particular, the Action asserts that Nelson explain that the roles of caveolin in prostate cancer are not clearly defined. Applicant submits that the Tahir article, which includes *in vivo* data showing that caveolin directly contributes to the growth and size of tumors, obviates the argument that the role of caveolin in prostate cancer is "not clearly defined." Applicant also relies upon the distinctions pointed out between the cited references and the current disclosure as stated in the previous response and respectfully requests withdrawal of the rejection.

Applicant respectfully submits that all the Examiner's concerns have been fully addressed and overcome, and that the claims are fully enabled. Applicant further requests withdrawal of all rejections under §112.

Applicant respectfully submits that the pending claims are in condition for allowance, and solicit an early indication to that effect. Should the Examiner have any questions, comments or suggestions that would more quickly progress the claims to allowance, the Examiner is invited to contact the undersigned representative at 512.542.8446.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Timothy S. Corder", written in a cursive style.

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